REMARKS

1. Prior Art Issues

The independent claim (14) recites that the calcium-binding compound is "encapsulated by a calcium-free membrane material". According to Webster's New Twentieth Century Dictionary Unabridged (2d ed), "encapsulate) means "to enclose in a capsule". The word "enclose", in turn, means (1) "to surround; to shut in; to hem in; to fence in; to confine on all sides"; (2) "to put into a receptacle"; (3) "to insert in an envelope..."; or (4) "to contain".

The term "membrane" is consistent with this reasoning. A "membrane" is a "thin, soft, pliable sheet or layer... serving as a covering a lining...."

It is quite plain that mixing or blending one compound with another is not the same as encapsulating one compound with another.

Claims 14, 18, 25, 28-30 and 35 are rejected as anticipated by Ashmead; 14, 25, 28, 29 and 35 as anticipated by Polok; all examined claims as anticipated by or obvious over Balkus; and 14, 18, 19, 25, 28 and 29 as anticipated by "Muzinre" [sic, Huzinec].

1.1. Ashmead

The reference describes several compositions, among which are compositions of EDTA, sodium tripolyphosphate and carboxymethylcellulose. The function of the carboxymethylcellulose is described at col. 3, lines 4-18. The carboxymethylcellulose is not used to encapsulate the EDTA, in fact it is stated in col. 3, lines 51-52 that the ingredients are blended together, and further in col. 3, line 59, that they may be dosed in the form of capsules or tablets. Thus, the reference does not disclose a product wherein EDTA is encapsulated in a cellulose, and therefore the present invention is not anticipated by Ashmead.

1.2. Polok

The reference describes compositions comprising a variety of compounds, among others zeolite. It is described that the compounds may be used or administered in combination with a mucoadhesive, wherein the mucoadhesive may be selected from for example a cellulose. No specific combination of zeolite and cellulose is disclosed. Furthermore, it appears as if the Examiner read "encapsulating" into the term "mucoadhesive". However, mucoadhesive does not mean encapsulated. Mucoadhesion is for example discussed in the enclosed article of Jasti et al.

A mucoadhesive preparation is a preparation which upon contact with an intact mucous membrane adheres to said mucous membrane for a sufficient time period to induce the desired therapeutic effect. The preparation can be a tablet, a powder, a gel or film comprising a mucoadhesive matrix or a syrup that adheres to the mucous membrane.

At page 195 of the Jasti article, it is explained, that matrix and membrane systems are known.

This means, that mucoadhesives are not limited to encapsulated formulations, and it is further substantiated by the fact, that Polok at col. 6, lines 31-38 mentions a variety of formulations, such as tablets, capsules, suspensions, slurries etc.

Accordingly, first of all Polok does not disclose a combination of a zeolite with a cellulose, and second the celluloses mentioned are used as mucoadhesives, not as encapsulating materials.

1.3. Balkus

The reference describes compositions using clay-enclosed paramagnetic ions as image contrasts agents. Thus the composition comprises paramagnetic ions encapsulated in clay. This is seen, i.a. at col. 2, lines 43-44, col. 3, lines 14-15

and 67-68, and col. 4, lines 49-50. At col. 5, lines 56-58 it is explained, that "..In preferred practice, zeolite or clay enclosed trivalent gadolinium is prepared in a pharmaceutical carrier prior to administration". However, there is no description of encapsulating the clay or zeolite.

In the following paragraph it is described that the zeolite or clay enclosed metal ion compounds may be combined with pharmaceutically acceptable formulating agents, dispersing agent and fillers, and in the following sentences a long list of formulations as well as a long list of formulating agents is discussed. However, there is no discussion of capsules or coated tablets wherein the capsule or coating is calcium-free. On the contrary both calcium-containing and calcium free materials are mentioned as formulating agents.

The Examiner's reference to "coated tablets of cellulose of Zeolites or clays" at "col. 5, top of 6" cannot be found in the entire document. Nowhere is it shown that the clay-enclosed paramagnetic ion may be coated with cellulose.

What is stated is the following:

In one sentence: list of preparations including coating and capsules

In another sentence: list of formulating agents including cellulose.

There is however no reference in the document that cellulose may be used for the coating. This combination is read into the document by the Examiner, but there is no basis for such interpretation of the document.

Accordingly, the present invention is neither anticipated nor obvious in view of Balkus.

1.4. Huzinec et al.

The reference describes a comestible product having extended release of additives. It is described in the Background of the

reference, that "..Encapsulation of additives such as flavors and sweeteners is time-consuming and expensive. In addition, the encapsulation process and parameters can change the character of the flavor...." Accordingly, Huzinec et al. teaches against encapsulation. Furthermore, there is no description of encapsulated clay or zeolite products in the reference.

The Examiner refers to col. 2, lines 16-18, however the Examiner misreads the text. The reference discusses the carrier for use in the comestible product. The carrier may be selected from a cellulose, zeolites, aluminum silicates, carbon black and mixtures thereof.

The carrier has an ability to incorporate the additives into the carrier by absorption and/or adsorption, see col. 2, lines 8-10.

The carrier selected from these materials may contain materials that aid in providing desirable properties, e.g. dispersants, such as ....gum arabic...., see col. 2, lines 13-16. There is no description hinting to the carrier being encapsulated in the dispersants.

Furthermore, in col. 2, lines 20-23 it is described that the carrier and additives are mixed leading to a carrier/additives "blend". There is no indication in the text that "blend" should be read as one compound encapsulating the other compound.

Thus, Huzinec et al. does not describe zeolites coated with gums, and therefore the claims are not anticipated by Huzinec et al.

1.5. Conclusion

None of the references cited by the Examiner anticipates the invention nor makes the invention obvious.

2. Description Issue

The Examiner says that "there is insufficient description

in the specification for one in the art to choose a Ca free form of fat, soap, stearate, and gum- one would find these components to incorporate (a) at least in small amounts".

While the Examiner has based this rejection on the "description" requirement of 35 USC 112 ¶1, a "calcium-free membrane material" was plainly described, see, e.g., page 7, line 30. It appears that the Examiner may have intended to raise an enablement issue. The Examiner is respectfully reminded that while the enablement requirement also derives from 35 USC 112 ¶1, it is a distinctly different requirement with a different standard.

To expedite prosecution, we respond to the implied enablement rejection, too.

Fats, stearates, and gums are normally calcium-free. With respect to soaps, the person skilled in the art knows how to produce soap from for example potassium hydroxide and fat instead of calcium hydroxide and fat, thus the person skilled in the art has enough information in this regard.

3. Definiteness Issues

3.1. The Examiner says that "one would not consider a clay mineral to include a zeolite". However, original claims 17-19, and P6, L12 and 17 of the disclosure, all identified the invention as encompassing clay minerals, including zeolites.

We are willing to defer to the Examiner's distinction between clay minerals and zeolites, provided that both are then separately claimed.

Consequently, we have amended claim 14 to recite zeolites, which then provides antecedent basis for "zeolites" in claim 31.

3.2. Claims 18 and 19 have been amended to depend from claim 14 rather than from cancelled 17.

3.3. With regard to claim 14, the absorbable citrate from and phosphate form may be absorbable in ionic form, but certainly

not absorbable when bound to calcium, thus the Examiner's objection is wrong.

Claim 15 recites encapsulation, already recited in 14, and hence is redundant. So we have cancelled 15.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By:_____
Iver P. Cooper
Reg. No. 28,005

Enclosure
-Jasti et al.

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
G:\ipc\g-i\hoib\Jorgensen2\ptoamend3.wpd

Recent Advances in Mucoadhesive Drug Delivery Systems

a report by

Drs Bhaskara Jasti, Xiaoling Li *and* **Gary Cleary**

Thomas J. Long School of Pharmacy & Health Sciences, University of the Pacific, and Corium International, Inc.

Dr Bhaskara Jasti is Assistant Professor of Pharmaceutics for the Department of Pharmaceutics and Medicinal Chemistry at Thomas J. Long School of Pharmacy & Health Sciences at the University of the Pacific (UOP). His research interests are in the design, development and evaluation of controlled release and targeted drug delivery systems, bioavailability classification, evaluation and *in vitro* and *in vivo* correlation (as per US Food and Drug Administration (FDA) guidelines) of oral, topical and novel drug delivery systems and clinical and metabolic investigation of anticancer agents. Dr Jasti has a PhD from UOP (1995), an MS in Pharmacy from Jadavpur University (1990) and a BS in Pharmacy from Kakatiya University, India (1987).

Dr Xiaoling Li is Associate Professor of Pharmaceutics, Chairman of the Department of Pharmaceutics and Medicinal Chemistry and Director of the Pharmaceutical and Chemical Sciences Graduate Program at Thomas J. Long School of Pharmacy & Health Sciences at the UOP. Dr Li has a PhD from the University of Utah (1991), an MS from Shanghai First Medical College, PR China (1985) and a BS from Shanghai First Medical College (1982).

Dr Gary Cleary is President and Chief Technical Officer of Corium International, Inc., a company that develops and manufactures film products for use in dermal, transdermal, consumer products, cosmetics/cosmeceuticals, diagnostic and electrotherapy applications. He is also the founder and Chairman Emeritus of Cygnus, Inc. His professional affiliations include the Controlled Release Society (Past President 1999–2000), American Association of Pharmaceutical Scientists, The New York Academy of Sciences, American Association for the Advancement of Science, Rho Chi and Sigma Xi. Dr Cleary obtained his PharmD from the University of California at San Francisco, his PhD in Pharmaceutics from Rutgers University, and his MBA in Health Sciences from the University of Miami.

Introduction

Transmucosal delivery of therapeutic agents is a popular method because mucous membranes are relatively permeable, allowing for the rapid uptake of a drug into the systemic circulation and avoiding the first pass metabolism. This efficient uptake offers several benefits over other methods of delivery and allows drugs to circumvent some of the body's natural defence mechanisms. The market share of transmucosal drug delivery systems has been increasing, with an estimated US market share of US$179 million in 2000. Transmucosal products can be designed to be administered via the nasal route by using sprays, pumps and gels, via the oral/buccal route using mucoadhesives, quick dissolve tablets and solid lozenge formulations and via vaginal or urethral routes using suppositories.[1]

In the development of these drug delivery systems, mucoadhesion of the device is a key element. The term 'mucoadhesive' is commonly used for materials that bind to the mucin layer of a biological membrane. Mucoadhesive polymers have been utilised in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosae. These dosage forms include tablets, patches, tapes, films, semisolids and powders. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups, suitable surface property for wetting mucus/mucosal tissue surfaces and sufficient flexibility to penetrate the mucus network or tissue crevices.[2]

Mucoadhesion

Many theories have been proposed to describe mucoadhesion, namely electronic theory, adsorption theory, wetting theory, diffusion theory and fracture theory. Mucoadhesion is believed to occur in three stages: wetting, interpenetration and mechanical interlocking between mucin and polymer. According to electronic theory, mucoadhesion occurs from the formation of an electric double layer at the mucoadhesive interface by the transfer of electrons between the mucoadhesive polymer and the mucin glycoprotein network.[3] Adsorption theory states that mucoadhesive systems adhere to tissue through secondary molecular interactions such as van der Waals forces and hydrogen bonding.[4] Intimate molecular contact is a prerequisite for the development of strong adhesive bonds, where wetting equilibrium and the dynamic behaviour of the bioadhesive polymeric material with the mucus is critical. The interfacial energetics is responsible for the contact of the two surfaces and the adhesive strength. Finally, diffusion theory states that interpenetration of the chains of polymer and mucus may lead to sustained mucoadhesion and by mechanical interlocking between mucin and mucoadhesives.[5]

Hydrocolloids are believed to adhere to mucosa upon hydration, as the synthetic polymer molecules become more freely mobile and are able to orientate adhesive sites favourably with those of the substrate. As the level of hydration increases, adhesive strength was found to decrease, since mucoadhesive bonds become overextended. It is proposed that the hydrogen bond-forming capacity of the polymer is important in this effect, and may emphasise the well-documented mucoadhesive properties of polymers possessing numerous carboxyl groups such as carbopol and polycarbophil. However, the greater swelling properties of the polymer-increased ionisation may lead to a reduction in mechanical strength and concomitant reduction in mucoadhesive properties. Based on the mucoadhesion theories, it may be concluded that the most efficient

1. *I W Kellaway and S J Warren (1996), "Mucoadhesive hydrogels for buccal delivery",* Oral Mucosal Drug Delivery, *(Ed. M J Rathbone), New York: Marcel Dekker Inc., pp. 221–239.*
2. *V Lenaerts and R Gurny (1990),* Bioadhesive Drug Delivery Systems, *CRC Press, pp. 25–42 and 65–72.*
3. *J R Huntsberger (1967),* Treatise on adhesion and adhesives, *(Ed. R Patrick), Vol. 1, New York: Marcel Dekker Inc.*
4. *A G Mikos and N A Peppas, "Measurement of the surface tension of mucin solutions",* Int. J. Pharm., *53 (1989), pp. 1–5.*
5. *S S Voyutskii (1963),* Autohesion and adhesion of high polymers, *New York: Wiley.*

mucoadhesive polymers have physiochemical properties that are closely related to those of the mucus substrate.

Mucoadhesive Polymers

Diverse classes of polymers have been investigated for potential use as mucoadhesives. These include synthetic polymers such as poly(acrylic acid) (PAA), hydroxypropyl methylcellulose and poly(methyl-acrylate) derivatives, as well as naturally occurring polymers such as hyaluronic acid and chitosan. Among these various possible bioadhesive polymeric hydrogels, PAA has been considered as a good mucoadhesive. However, due to a high transition temperature and higher interfacial free energy, PAA does not wet the mucosal surface to the optimal level, causing loose interpenetration and interdiffusion of the polymer. Therefore, PAA is copolymerised with polyethylene glycol (PEG) or poly(vinyl pyrrolidone) (PVP) to improve these properties. It is important to realise that balanced adhesive and cohesive properties for a polymer is essential for its application in a transmucosal drug delivery system, especially for the removable devices.

Devices

Bioadhesive dosage forms, such as laminated polymer films,[6] mucoadhesive tablets[7,8] and patches[9], are currently being investigated for sustained delivery of drugs. Several laminated devices have been developed to achieve sustained drug release. These include devices containing an impermeable backing layer, a rate-limiting membrane and an adhesive polycarbophil layer (which remained in place for 17 hours in dogs and humans),[10] two polylaminates consisting of an impermeable backing layer and a hydrogel-containing drug,[11] and a dosage form comprising a non-adhesive backing, a drug core and a peripheral adhesive layer.[12]

Based on the mechanism by which a drug is released, the devices can be classified into one of the following two categories:

- monolithic (or matrix) systems where the drug is dissolved or dispersed in the polymer system – diffusion of drug from the drug/polymer matrix controls the overall rate of its release from the device; and
- reservoir (or membrane) systems where diffusional resistance across a polymeric membrane controls the overall drug release rate.

The selection of either a monolithic or reservoir system for transmucosal delivery depends on the major limiting factor that controls the rate of drug transport and its delivery to the systemic circulation. When the desired rate of drug transport is considerably less than that through the mucosal membrane, a device control of drug delivery is required to attain therapeutic steady-state concentrations of drug in the plasma and to prevent overdosing. In such cases, a device with a rate-controlling membrane is needed. On the other hand, if drug permeation through the mucosal membrane is the rate-controlling step, a monolithic or matrix type of delivery system is sufficient.

Novel Mucoadhesive Polymers Under Development

For optimal buccal mucoadhesion, Shojaei and Li have designed, synthesised and characterised a copolymer of PAA and PEG monoethylether monomethacrylate (PAA-co-PEG) (PEGMM).[11] By adding PEG to these polymers, many of the shortcomings of PAA for mucoadhesion, outlined earlier, were eliminated. Hydration studies, glass transition temperature, mucoadhesive force, surface energy analysis and effect of chain length and molecular weight on mucoadhesive force were studied. The resulting polymer has a lower glass transition temperature than PAA and exists as a rubbery polymer at room temperature. Copolymers of 12 and 16-mole %PEGMM showed higher mucoadhesion than PAA. The effects of hydration on mucoadhesion seen by the copolymers revealed that film containing lower PEGMM content, which had higher hydration levels, had lower mucoadhesive strengths. The 16-mole

6. *Y Kohda, H Kobayashi, Y Baba, H Yuasa, T Ozeki, Y Kanaya and E Sagara, "Controlled release of lidocaine HCl from buccal mucosa-adhesive films with solid dispersion"*, Int. J. Pharm., *158 (1997), pp. 147–155.*
7. *A Ahuja, R Khar and R Chaudhry, "Evaluation of buccoadhesive metronidazole tablets: microbiological response"*, Pharmazie, *53 (1998), pp. 264–267.*
8. *P Minghetti, A Colombo, L Montanari, G Gaeta and F Gombos, "Buccoadhesive slow release tablets of acitretin: design and in vivo evaluation"*, Int. J. Pharm., *169 (1998), pp. 195–202.*
9. *J Guo, "Bioadhesive polymer buccal patches for buprenorphine controlled delivery: formulation, in vitro adhesion and release properties"*, Drug Dev. Ind. Pharm., *20 (1994), pp. 2,809–2,821.*
10. *M Veillard, M A Longer, T W Martens and J R Robinson, "Preliminary study of oral mucosal delivery of peptide drugs"*, J. Control. Rel., *6 (1987), p. 123.*
11. *A M Shojaei and X Li, "Mechanisms of buccal mucoadhesion of novel copolymers of acrylic acid and polyethylene glycol monoethylether monomethacrylate"*, J. Control. Rel., *47 (1997), pp. 151–161.*

%PEGMM had the most favourable thermodynamic profile and the highest mucoadhesive forces. Polymers investigated in this study also showed that the molecular weight and chain length had little or no effect on the mucoadhesive force.

Novel polymers of PAA complexed with PEGylated drug conjugate were investigated by Lele, et al.[13] Only a carboxyl group containing drugs such as indomethacin could be loaded into the devices made from these polymers. An increase in the molecular weight of PEG in these copolymers resulted in a decrease in the release of free indomethacin, indicating that drug release can be manipulated by choosing different molecular weights of PEG.

A new class of hydrophilic pressure-sensitive adhesives (PSAs) that share the properties of both hydrophobic PSAs and bioadhesives has been developed by Corium Technologies.[14] These Corplex™ adhesive hydrogels have been prepared by non-covalent (hydrogen bond) cross-linking of a film-forming hydrophilic polymer (for example PVP) with a short-chain plasticiser (typically PEG) bearing complementary reactive hydroxyl groups at its chain ends. Owing to the appreciable length and flexibility of PEG chains, a relatively large space can be provided for a stoichiometric complex and a 'carcass-like' structure. The specific balance between enhanced cohesive strength and large free volume in PVP–PEG miscible blends influences their PSA behaviour. Properties of these hydrophilic PSA hydrogels prepared by the carcass-like cross-linking method can be modified using a polymer with complementary reactive groups to form 'ladder-like' cross-links with PVP. Thus, these Corplex™ PSA hydrogels have a broad range of unique adhesive/cohesive properties that enable topical and drug delivery systems to be applied to either skin or mucosa.

An AB block copolymer of oligo(methyl methacrylate) and PAA has been synthesised for prolonged mucosal drug delivery of hydrophobic drugs.[15] These block copolymers form micelles in an aqueous medium, which was confirmed by a fluorescence probe technique using pyrene. A model drug, doxorubicin hydrochloride, when incorporated into these micelles, results in its release being prolonged at a slower rate.

Polymers with thiol groups were also investigated as a new generation of mucoadhesive polymers. A study conducted by Bernkop-Schnurch, et al. demonstrated that introduction of a sulphahydryl group increased the adhesive properties of mucoadhesive polymers.[16] In this study, cysteine was attached covalently to polycarbophil by using carbodiimide as a mediator, forming amide bonds between the primary amino group of the amino acid and the carboxylic acid moieties of the polymer. The results showed that there was considerable improvement in the overall behaviour of adhesion and adhesive properties when tested on porcine intestinal mucosa at a pH level above five.

In addition, mucoadhesive microspheres were studied recently by Bogataj, et al. for application in the urinary bladder.[17] The microspheres were prepared by a solvent evaporation method using Eudragit RL or hydroxypropylcellulose as matrix polymers. In another study, microspheres with a Eudragit RS matrix polymer and different mucoadhesive polymers, i.e. chitosan hydrogen chloride, sodium salt of carboxymethyl cellulose and polycarbophil were prepared and found to be useful as platforms for oral peptide delivery, with a high capacity of binding to bivalent cations, which are essential cofactors for intestinal proteolytic enzymes.[18]

Summary

Mucoadhesive drug delivery systems are being studied from different angles, including development of novel mucoadhesives, design of the device, mechanisms of mucoadhesion and permeation enhancement. With the influx of a large number of new drug molecules from drug discovery, mucoadhesive drug delivery will play an even more important role in delivering these molecules. ■

12. *T Nagai and R Konishi, "Buccal/gingival drug delivery systems"*, J. Control. Rel., *6 (1987), p. 353.*
13. *B S Lele and A S Hoffman, "Mucoadhesive drug carriers based on complexes of poly(acrylic acid) and PEGylated drugs having hydrolysable PEG-anhydride-drug linkages"*, J. Control. Rel., *69 (2000), pp. 237–248.*
14. *G W Cleary, M M Feldstein, P Singh and N A Platé, "A New Polymer Blend Adhesive With Combined Properties to Adhere to Either Skin or Mucosa for Drug Delivery", Podium Abstract, 30th Annual Meeting and Exposition of the Controlled Release Society, Glagsow, Scotland, 19–23 July 2003.*
15. *T Inoue, G Chen, K Nakamae and A S Hoffman, "An AB copolymer of oligo (methyl methacrylate) and poly(acrylic acid) for micellar delivery of hydrophobic drugs"*, J. Control. Rel., *51 (2–3) (1998), pp. 221–229.*
16. *A Bernkop-Schnurch, V Schwarch and S Steininger, "Polymers with thiol groups: A new generation of mucoadhesive polymers?"*, Pharm. Research, *16 (6) (1999), pp. 876–881.*
17. *M Botagataj, A Mrhar and L Korosec, "Influence of physiochemical and biological parameters on drug release from microspheres adhered on vesical and intestinal mucosa"*, Int. J. Pharm., *177 (1999), pp. 211–220.*
18. *H Chen and R Langer, "Oral particulate delivery: status and future trends"*, Adv. Drug Delivery Rev., *34 (1998), pp. 339–350.*